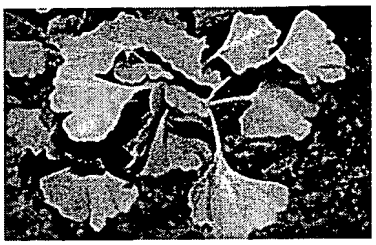
Ginkgo biloba - A Short Review

by Hans Wohlmuth



History and botany

The maidenhair tree (*Ginkgo biloba* L.) is often referred to as a 'living fossil'. This term refers to the ancient origin of the lineage of which *Ginkgo biloba* is the only living representative. The genus Ginkgo appears to date back to the lower Jurassic, about 190 million years ago, and while *Ginkgo biloba* certainly is much younger than that, fossil material from another Ginkgo species from the early Cretaceous (about 180 million years ago) closely resembles *Ginkgo biloba* (1).

Taxonomically, *Ginkgo biloba* is the single most unique plant in the world today, being the only existing member of the division Ginkgophyta (2). In China and Japan the tree has been cultivated in temple gardens for many centuries. It was introduced to Europe from the far East around 1730 and is now widely cultivated in many countries around the world (3).

The question of whether any wild populations of *Ginkgo biloba* still exist has been debated by botanists for a very long time and remains unanswered. The best candidate for a remnant wild population is a stand of some 160 trees in the Tian Mu Shan Reserve in Zhejiang province in China (1).

In China, the cultivation of *Ginkgo biloba* for at least 1,000 years is documented. It was grown primarily for its edible and medicinal 'nuts' (1).

The use of ginkgo leaf

In contrast to the seed, ginkgo leaf was never extensively used in Traditional Chinese Medicine (TCM) and was not included in any Chinese Pharmacopoeia or any other classic text on TCM. However, ginkgo leaf is claimed to have been used for cardiovascular disorders and asthma in Chinese folk medicine, allegedly from about 1550 AD (3) .

The medicinal use of ginkgo seed was first mentioned in European herbals in the 1800s, but the use of ginkgo leaf preparations did not become widespread until after 1965, when ginkgo extracts were introduced into medical practice in Germany (3) .

Active constituents (3)

Ginkgo leaf contains a variety of chemical compounds, including sesqui-, di- and triterpenes, flavonoids, organic acids, proanthocyanidins, steroidal compounds, a polyphenol, and sugars.

The 5 highly oxidised diterpenes known as ginkgolides are unique trilactone molecules of a semispherical shape. They are stable, crystalline substances that are soluble in a variety of organic solvents and moderately soluble in hot water. Ginkgo leaves contain less than 0.1% ginkgolides. Bilobalide is a sesquiterpene trilactone.

Different types of flavonoids occur in ginkgo leaves including dimeric flavonoids, flavonols and flavonol glycosides, coumaric esters of flavonol glycosides, flavones and flavone glycosides, catechins, and oligomeric and polymeric procyanidins.

Standardised ginkgo extracts

Products based on standardised ginkgo leaf extracts are widely available to both the public and healthcare professionals.

Extensive research has been carried out on standardised extracts, and the current clinical use of ginkgo is based on this research, not on traditional use.

Ginkgo is probably the most thoroughly researched plant used in contemporary Western herbal medicine. Ginkgo extracts are standardised to 24% ginkgo flavonolglycosides (ginkgo flavonglycosides) and 6% terpene trilactones (ginkgolides and bilobalide).

The content of the allergenic anacardic acid should be 5 ppm or less. Standardised extracts of ginkgo leaf are highly concentrated, with a herb to extract ratio of 35-67:1 (on average 50:1) (4).

Pharmacology

The pharmacology of ginkgo extracts has been studied extensively, and many types of pharmacological activity have been demonstrated.

The main actions have been classified into two main areas: vaso- and tissue-protective effects and cognition-enhancing effects (3) .

Central to both types of action may be the antioxidant and free radical scavenging properties of ginkgo extract, which is probably due to the flavonoids.

Oxidative damage is known to play a role in many disease processes including vascular disease, and there is mounting evidence that oxidative stress may play an important role in the pathogenesis of Alzheimer's disease (5).

Ginkgo extracts have demonstrated scavenging activity against a variety of reactive oxygen species, including the superoxide radical and the hydroxyl radical (3). Many compounds isolated from ginkgo are antagonists of platelet-activating factor (PAF), the most potent being ginkgolide B (3).

PAF is not only involved in platelet aggregation but also in inflammation, bronchoconstriction and microvascular permeability.

The vasorelaxing effect of ginkgo extracts may involve the endothelial derived relaxing factor (now identified as nitric oxide) and prostacyclin (3) . It is possible that ginkgo protects these compounds by way of its free radical scavenging activity.

Substantial experimental evidence suggests that ginkgo extract has neuroprotective action in cases of hypoxia, seizure activity and peripheral nerve damage (6).

Clinical uses

Clinical trials with standardised ginkgo leaf extracts have confirmed its place in the clinical treatment of cerebral

insufficiency, dementia, tinnitus, peripheral arterial occlusive disease and intermittent claudication.

Cerebral insufficiency and dementia

Cerebral insufficiency in elderly people is characterised by difficulties of concentration and memory, being absent minded, being confused, lack of energy, tiredness, decrease of physical performance, depressive mood, anxiety, dizziness, tinnitus and headaches (4) .

A critical review of 40 trials was published in 1992 (4) . Only 8 of these trials were deemed to be well performed. Virtually all trials reported positive results with ginkgo treatment. In most trials the daily dose was 120-160 mg standardised extract, administered for at least 4-6 weeks.

Since 1994, four randomised, double-blind, placebo-controlled trials of ginkgo in patients with Alzheimer's disease and/or multi-infarct dementia have been published.

The efficacy of ginkgo extract in 216 outpatients with presenile and senile primary degenerative dementia of the Alzheimer type and multi-infarct dementia according to DSM-III-R was investigated in a prospective multi-centre study (7) .

After a 4-week run-in period, subjects were randomised to receive a dose of 120 mg standardised ginkgo extract twice daily or placebo for a 24-week treatment period.

Primary outcome variables were the Clinical Global Impressions for psychopathological assessment, assessment of attention and memory, and behavioural assessment of daily life activities. Clinical efficacy was defined as response in at least two of the three primary outcome variables.

The proportion of treatment responders was significantly higher in the ginkgo group than in the placebo group (28% vs 10%, p=0.005). Intention-to-treat analysis yielded a similar result in favour of the ginkgo treatment (p=0.012).

In another multi-centre study, 309 mildly to severely demented outpatients with Alzheimer's disease or multi-infarct dementia were enrolled to receive either ginkgo standardised extract (40 mg 3 times daily) or placebo for 52 weeks (8) 202 patients completed the study. In the intention-to-treat analysis, the ginkgo group scored significantly better than placebo on a cognitive assessment scale (p=0.04) and a relative's rating scale (p=0.004).

Of the patients who completed the 52-week trial, 27% on ginkgo improved by at least 4 points on the cognitive scale compared with 14% taking placebo (p=0.005); 37% of the ginkgo group improved on the relative's rating scale compared with 23% of the placebo group (p=0.003).

No significant effect of ginkgo treatment was seen on the Clinical Global Impression of Change scale.

The authors concluded that ginkgo can stabilise, and in a substantial number of cases, improve, cognitive performance and social functioning of demented patients.

Ginkgo extract (80 mg three times daily for three months) versus placebo was studied in forty hospitalised patients suffering from incipient senile dementia of the Alzheimer type (9) . Ginkgo treatment provided a highly significant improvement in memory and attention compared with placebo after one month (17). This effect was maintained for the 3 months' duration of the trial.

Thirteen of 18 items on a geriatric clinical assessment scale improved significantly. Ginkgo treatment was found to be superior to placebo with respect to cognitive disturbances, emotional disturbances, lack of drive, social behaviour and somatic disturbances.

A small study involving 20 outpatients suffering from mild to moderate dementia of the Alzheimer type investigated the effects of ginkgo standardised extract (80 mg 3 times daily) versus placebo for 3 months (10) .

The primary outcome variables were attention and memory. Ginkgo treatment produced a significantly better effect than placebo ($p<0.013$).

Most recently, Ernst and Pittler have published a systematic review of clinical trials investigating the efficacy of ginkgo extract in dementia (11) .This review included 9 double-blind placebo-controlled trials and concluded that ginkgo is more effective for dementia than placebo.

A recent placebo-controlled study investigated the effects of ginkgo extract (120 mg or 240 mg daily for 3 months) on cognitive function and blood pressure in 60 elderly subjects with mild to moderate cognitive impairment (12) . Attention, concentration and short-term verbal memory improved significantly and diastolic blood pressure decreased significantly with low-dose ginkgo treatment.

Tinnitus

One randomised, double-blind, placebo-controlled trial of ginkgo standardised extract (160 mg/day for 3 months) in 103 out-patients suffering tinnitus of recent 1 year onset found ginkgo treatment to positively affect the overall evolution of the condition, compared with placebo ($p=0.05$) (13) .

Median time to disappearance or distinct improvement of tinnitus symptoms was 70 days in the ginkgo group and 119 days in the placebo group ($p=0.03$).

Sprenger (1986) reported improvements in hearing and reductions in tinnitus from a 9-week open trial in 62 patients with inner-ear difficulties (14) .

Clinical studies into the efficacy of ginkgo in tinnitus have also yielded negative results.

A double-blind placebo-controlled crossover study of a ginkgo extract (29.2 mg daily for 2 weeks) found no effect over placebo in 20 patients suffer-ing persistent severe tinnitus (15) .

Similarly, an open study with 23 mostly long-standing (median 8.5 years) tinnitus patients taking 120 mg ginkgo extract daily for 12 weeks found no statistically significant evidence for an effect of the treatment (16) .

Peripheral arterial occlusive disease and intermittent claudication

Fifteen controlled trials of ginkgo extract for intermittent claudication (a deficiency of blood supply in exercising muscle) were identified by a critical review in 1992, but only two of these trials were deemed to be of acceptable quality (17) .

All trials were positive; of the two best quality trials, one showed statistically signifi-cant improvements in walking distance from 112 m to 222 m on ginkgo treatment (120 mg/day for 6 months), compared with from 145 m to 176 m on placebo (18) .

The other trial showed ginkgo to ameliorate pain at rest; ginkgo for 8 days caused a decrease on a 100 mm visual analogue scale for pain from 61 to 30 mm, compared with a decrease from 51 to 39 mm for placebo (19) .

In a small, randomised, placebo-controlled, double-blind study with 20 patients suffering from claudicating atherosclerotic arterial occlusive disease (stage II), patients took ginkgo standardised extract (160 mg twice daily) or placebo for 4 weeks (20) .

The anti-ischaemic effect was monitored by measuring the transcutaneous partial pressure of oxygen during exercise on a treadmill. Ginkgo treatment decreased ischaemic areas by 38%, while placebo resulted in a 5% increase ($p=0.04$).

In the most recent trial to be published, ginkgo treatment was compared with placebo over 24 weeks in 111

patients with peripheral occlusive arterial disease (stage II b) (21) .

The pain-free walking distance increased significantly more in patients on ginkgo treatment than in patients on placebo (p=0.016).

Safety

Ginkgo has been well tolerated in numerous clinical trials. In recent years, however, at least 5 reports of abnormal bleeding associated with ginkgo use have appeared in the medical literature.

It is premature to conclude that the therapeutic use of ginkgo extract increases the risk of haemorrhage. The reports must be seen in the context of the current wide-spread use of ginkgo.

Also, ginkgo is mostly taken by elderly individuals who are more likely to experience abnormal bleeding events. However, these reports should serve to put practitioners and authorities on the alert, and it is important that future adverse reactions to ginkgo extracts be reported, so that an accurate safety profile can be established.

Until this happens, it would be prudent to take particular care when prescribing ginkgo extract to patients on anticoagulant medication, including long-term aspirin.

Dosage

Most clinical trials have used standardised ginkgo extract in a dose of 120-160 mg daily. Some studies have used a dose of 240 mg daily. The majority of the clinical studies carried out in Europe have used Schwabe's extract, EGb761® or Indena's GinkgoSelect™. Both extracts are covered by patents.

Statistical Significance

The statistical signifigance of a finding is often expressed as a p-value.

"P" stands for probability, and the p-value indicates the probability that the finding was due to chance.

Therefore, the smaller the p-value, the more confident one can be that the observed effect was real, and not simply a result of chance events.

Generally a finding is said to be statistically significant if the p-value is 0.05 or less, ie there is only a 5% (1 in 20) chance or less that the observed effect was due to chance.

Therefore if p=0.001, there is only a 1 in 1000 chance that the effect was due to chance, or if p=0.0001, there is only a 1 in 10000 chance that the effect was due to chance.

That is, the lower the value of "p", the more significant the result becomes.

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Articles in this issue:


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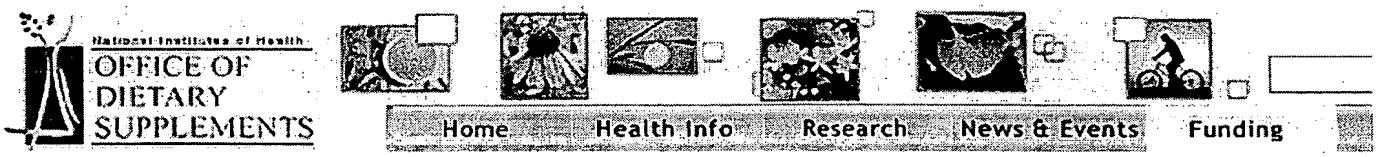

ODS Cofunded Grant Abstracts

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Grant Number: **1 R01 MH068817-01**
PI Name: Nakanishi, K.
Project Title: Neuromodulatory Effects of Ginkgolides and Bilobalide

Abstract: DESCRIPTION (provided by applicant): This proposal is focused on the mode of action of the ginkgolides and bilobalide (terpenoid trilactones) from the tree Ginkgo biloba. The crude extract of G. biloba, a complex mixture composed of many different compounds, have shown effects on the diseased as well as healthy state of the mammalian brain. Clinical studies, animal studies, and various in vitro studies of the extracts have demonstrated beneficial effects against various neurodegenerative diseases, particularly Alzheimer's disease, as well as memory enhancing effects in the normal brain. However, very little is known about effects of individual constituents, especially at the molecular structural level. In this proposal, we will focus on the most unique constituents of the Ginkgo biloba extract, the ginkgolides and bilobalide, but not on the action of the crude extract which clearly involves synergistic effects, e.g., between the flavonoids (a major component) and the terpenoid trilactones. Some ginkgolides are antagonists of the platelet-activating factor receptor (PAFR), and appear to have antioxidant and neuroprotective properties. We have also found that ginkgolide B is a glycine receptor antagonist, while bilobalide is a potent GABAA receptor antagonist. Our goal is to determine the neuromodulatory effects of terpene trilactones on the mammalian central nervous system, using bioorganic and spectroscopic methods, including those under development in our laboratory on a molecular level. The specific topics to be studied include synthesis of radiotracers for positron emission tomography (PET) and ex vivo autoradiography studies, design and preparation of novel photolabile and fluorescent terpene trilactones analogs to be used to elucidate the interactions of terpene trilactones and PAFR. During these studies we will develop and apply novel methodologies such as ultra-microscale photolabeling and sequencing using unconventional mass spectrometric and circular dichroic techniques, as well as "membrane scissors". Using radioligand binding and microphysiometry, we will initiate studies on the effects of terpene trilactones on the cloned PAFR, using PAFR expressed in Chinese hamster ovary cells. The effects of terpene trilactones on long-term potentiation will be examined in vitro as well as in animal models. These studies can potentially provide new targets for terpene trilactones in the central nervous system that require the synthesis of new ginkgolide and bilobalide ligands.

Institution: COLUMBIA UNIV NEW YORK MORNINGSIDE
Project Start: 12-SEP-2003
Project End: 30-JUN-2008

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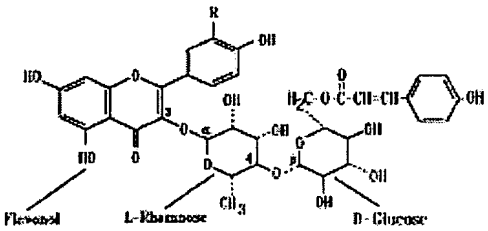
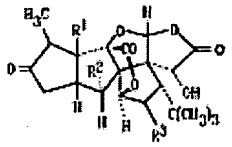


R	Flavonol
H	Kämpferol
OH	Quercetin



Ginkolide	R^1	R^2	R^3
A	OH	H	H
B	OH	OH	H
C	OH	OH	OH

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LINNEA INC (USA)

- Artichoke leaf extract 5%
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- Ginkgo biloba extract EPG 246
- Ginkgo biloba extract G 328
- Ginkgo biloba extract G 320
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- L-5-Hydroxytryptophan (Griffonia seed extract)

Request a technical data sheet for Ginkgo biloba extract

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Ginkgo biloba extracts EPG 246, G328 and G320

Chemical definition: Mixture of Ginkgo flavonol glycosides, Ginkgo terpene lactor Proanthocyanidins.

Assay:

- Linnea EPG 246: 24% Ginkgo flavonglycosides, 6% Terpene lactones (Gi and bilobalides balanced as per German monograph)
- Linnea G 328: 32% Ginkgo flavonglycosides, 8% Terpene lactones
- Linnea G 320: 32% Ginkgo flavonglycosides, without Terpene lactones (m in cosmetic applications)

Product Origins: Linnea Ginkgo Biloba Extracts EPG 246, G 328 and G 320 are e from the leaves of the Ginkgo Biloba tree dating from the Palaeozoic era (350 milli ago). The Ginkgo Biloba tree, which is notable for high resistance to both pollutant pests, has a long tradition of use in Oriental medicine; in particular for the treatmer control of respiratory and circulatory ailments and for brain function.

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Click here to view the Linnea Botanical Brief

The name Ginkgo is derived from a wrong transcription of the Japanese name Yin means silver fruit, while the name biloba derives from the bilobed shape of its leaf.

Among the pharmacological active constituents those compounds with great impor the flavonoids (ginkgo flavonol glycosides) and the terpene trilactones (ginkgolides bilobalide). Different kind of flavonoids has been isolated from the ginkgo extracts. therapeutic interest are glycosyl derivitives of quercitin and kaempferol respectivel Kaempferol is considered particularly relevant for the therapeutic efficacy.

Therapeutic Applications: Ginkgo biloba extract is believed to have a regulating the entire vascular system of veins, arteries and capillaries. The most common us Gingko biloba extract is for its widely accepted effects in the regulation of blood flo brain, legs and other extremities. Also commonly cited for the control of the level o

- Melilotus (Sweet yellow clover extract)
- Olive Leaf Dry Extract 18
- Pilocarpine hydrochloride (USP 24 - BP 2000 - PH. EU. III)
- Red Clover extract IFL 18
- Red Clover extract IFL 40
- Silymarin 80
- St John's Wort extract
- Timolol Maleate (USP 24 - BP 2000)
- Troxerutin
- Valerian Root Dry Extract
- Vincamine (Fr. Xe - DAC 86)
- Vinpocetine (JPC 1993)
- Yohimbine hydrochloride (DAC 86 - OAB 81 - HELV. VI - USP 25)
- Zea Mays insaponifiable fraction

neurotransmitters in the brain thus helping to counteract memory loss, depression alertness which may occur in old age.

A reported "smart drug" Ginkgo biloba extract may also promote the metabolism of and neurosensorial cells. Gingko biloba is also used to counteract a number of cor such as vascular insufficiency and tinnitus and has also been indicated in the treat intermittent claudication (pain while walking). Recent studies have also indicated th use of Ginkgo biloba in the treatment of AlzheimerXs disease. Ginkgo biloba extra free radical scavenger and powerful antioxidant.

Cosmetic Applications: Include anti ageing, elimination of toxins, free radical sca powerful antioxidant, strengthening of the skins defenses, improvement of dermal circulation and stimulation of lymph drainage.

Therapeutical Categories: Vasodilator, Anti-ischemic, Free radical scavenger &

Synonyms: Maidenhair Tree